IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Alan DRIZEN et al.

Serial No.: 08/796,578 Examiner: R. Harrison

Filing Date: February 6, 1997 Group Art Unit: 1616

For: **TOPICAL DRUG PREPARATIONS**

#11
Suggs
12-8-98

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Box AF
Washington, D.C. 20231

Sir:

I, Alan Drizen, a citizen of Canada, hereby declare that:

1. I have extensive experience in pharmacokinetics and areas relating to the development of drug delivery systems and, in particular, polymer-based drug delivery systems, as shown in the attached curriculum vitae (Attachment 1). I have had extensive experience in the development of hyaluronic acid-based products over the past twenty years. In particular, prior to my present position, I was with Hyal Pharmaceutical Corporation where I was engaged in the development of hyaluronic acid-based chemotherapeutic compounds for treatment of melanoma. Over the past twelve years, I have received four patents relating to hyaluronic acid-based products.

2. I am a joint inventor of the invention claimed in the above captioned United States Patent Application.

3. I have reviewed United States Patent Application Serial No. 08/796,578 and the following reference cited by the Examiner in the final Office Action: Leshchiner et al., U.S. Patent No. 5,143,724, issued September 1, 1992. The Leshchiner et al. reference is similar to other hyaluronic acid crosslinking technology patented by Balazs in U.S. Patent Nos. 4,713,448; 4,636,524; 4,605,691; and 4,582,865. I have also reviewed these patents by Balazs.

4. I am informed that the claims of this application were rejected on the grounds that the invention as claimed is obvious over Leshchiner et al.

5. In my opinion, based upon an examination of Leshchiner et al. and my extensive experience in the field of polymer drug delivery systems using hyaluronic and its salts, the polymer gel slurries disclosed in the reference are not the same systems as claimed in the present application, the reference is not capable of transdermal drug delivery and thus the reference is entirely inoperable with regard to transdermal drug delivery formulations as claimed in the present formulations.

6. The compositions disclosed by Leshchiner et al. are crosslinked polymers. Such polymers would not be effective for transdermal drug delivery. The hyaluronic acid derivative described in the reference is a highly modified polymer produced by a complex procedure

involving crosslinking with vinyl sulfone. This process drastically and dramatically changes the viscoelastic properties and ionic characteristics of sodium hyaluronate.

7. In examples 1 through 21, the reference discloses various properties of the described slurries made with highly modified crosslinked polymers. A comparison between the properties of crosslinked highly modified hyaluronic acid derivatives and the sodium hyaluronate recited in the present claims is impossible given that the two substances are as different as sodium chloride and sodium bicarbonate.

8. Close examination of Example 12 of the reference shows that crosslinking with vinyl sulfone was necessary in order to prepare the finished product which apparently consists of a mixed gel of crosslinked polymer and carboxymethyl cellulose (CMC). Following various processes to produce a viscous gel, the concentrated gel was reported to have polymer concentrations in the range of 0.32 to 0.49, various dynamic properties at 5 Hz and relaxation properties. The practical use of such a slurry is not identified and one can only assume that the experiment is designed to demonstrate certain physical properties as described previously to significantly altered polymers. Crosslinked polymers are not suitable for drug delivery or effecting the delivery of therapeutic agents including niacin, diclofenac, ibuprofen, ascorbic acid, etc., through the stratum corneum, epidermis and dermis of the skin.

9. Example 12 of the reference also requires CMC. The use of CMC in a 1:1 mixture with the modified polymer bears no relationship to the claimed transdermal formulation. Based on my first hand observations, when CMC is incorporated into the polymer matrix, even without crosslinking, transdermal drug delivery is not achieved. It is necessary for the claimed system to use highly purified pharmaceutical grade hydroxyethyl cellulose (HEC). Without this feature, there is no penetration of stratum corneum and other layers of the skin for delivery of therapeutic amounts of drug. Thus, the quality and non-ionic nature of the HEC is an integral part of the formulation and effectiveness of the present invention.

10. Another particularly important mechanism for drug delivery in the present system which is not addressed by Leshchiner et al. is the strong negative charge of the sodium hyaluronate required in the present application. The present invention requires a highly specific and exclusive property that relates to a specific grade of sodium hyaluronate which has a specific ionic charge. When combined in a matrix with pharmaceutical grade HEC (non-ionic polymer), the target therapeutic substance, e.g., diclofenac, ibuprofen, etc., is believed to be encapsulated or held by ionic bonds within the matrix formed by the present process.

11. Several features required to obtain transdermal drug delivery are not disclosed by Leshchiner et al. The ionic polymer principle, the relationship between the molarity and ionicity, and the specific ionic and non-ionic relationships are all important aspects of the

present invention and are not described by Leshchiner et al.

12. Leshchiner et al. emphasize the rheological properties for the crosslinked polymer of gel slurries. However, from a drug delivery perspective, the concentrations, viscoelastic properties and other described physical characteristics are irrelevant. No drug other than a similar class of slurry can be incorporated into these mixtures or combinations.

13. As the attached study (Attachment 2) illustrates, the composition claimed in the present application attains transdermal drug delivery when used with 3% diclofenac, a nonsteroidal anti-inflammatory analgesic (NSAID). Moreover, the efficacy of the claimed invention is unexpectedly superior to that of orally administered diclofenac. The graph entitled "Diclofenac Plasma Concentrations" on page 1, shows the levels of drug which followed the administration of 4 ml (120 mg) of diclofenac gel applied to the entire circumference of subjects' knees under the controlled conditions described in the attached protocol (Attachment 3). As the graph shows, drug is present in plasma generally after one hour, but peak plasma concentrations are reached in 16 hours. Oral dosing of diclofenac, on the other hand, produces a far different profile, as discussed in the attached report entitled "Diclofenac Sodium Delayed-Release Tablets" (Attachment 4). Oral diclofenac administered to patients has a half-life of only two hours.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: NOV. 26/98

Alan Drizen

GMX.SPY/122.dec

Attachment 1

CURRICULUM VITAE

ALAN DRIZEN

100 Canyon Avenue, Suite 1201
North York, Ontario, Canada
M3H 5T9

tel: (416) 636-2403

CURRICULUM VITAE

PERSONAL

Full Name:	Alan Drizen
Address:	100 Canyon Avenue, Suite 1201 North York, Ontario, Canada M3H 5T9
Telephone:	(416) 636-2403
Citizenship:	Canadian
Social Insurance No.:	424-664-779
Date of Birth:	May 24, 1939
Place of Birth:	London, England
Spouse's Legal Name:	Barbara Drizen
Spouse's Social Insurance No.:	461-156-911

EDUCATION

1952-1954	William Ellis College University of London, G.C.E. Advanced Level
1954-1960	University of London, England B.Sc., Biology and Chemistry

EMPLOYMENT HISTORY

1961-1964	New drug monitor. U.S.V. Corp, Toronto, Canada
1964-1970	Drug developmental specialist and consultant. Sterile Pharmaceuticals, Mississauga, Ontario, Canada

Employment History - continued

1970-1991		Founder, Director, and Chief Scientific Officer. Hyal Pharmaceutical Corp., Toronto, Canada
	Duties:	Overall responsibility for research programs for new drugs in the areas of drug development, clinical testing and regulatory approval from 1978-1991. Responsibility for sodium hyaluronate drug development program in partnership with Fidia Pharmaceuticals, Albarno Terme, Italy. Headed team that was responsible for gaining FDA approval for Synacid, a hyaluronic acid based product for intra-articular injection in 1986. In addition, Drizen and his team formulated all Hyal's oncology products which have subsequently been approved by various regulatory agencies around the world. Certain of these sodium hyaluronate based oncology products have received patent approval in a number of countries, including the European common market and Canada.
1991-1993		Pharmaceutical consultant to major corporations in Canada and the United States.
1994-Present		Chairman and C.E.O. of L.A.M. Pharmaceutical Corp.
	Duties:	Responsible for L.A.M. drug delivery systems and technology. Co-inventor of ionic polymer matrix technology in which both ionic and non-ionic polymer have a significant and highly specific function.

MEMBERSHIPS

Canadian Pharmaceutical Manufacturers Association
William Ellis Old Boys Club

Attachment 2

LAM Pharmaceuticals

SUBJECT: South Florida Bioavailability Clinic (SFBC) study LAM01 is a pilot, single dose, open label study to investigate the effects of 3% diclofenac nonsteroidal anti-inflammatory analgesic (NSAID) in LAM Pharmaceutical's IPM gel.

OBJECTIVE: To determine

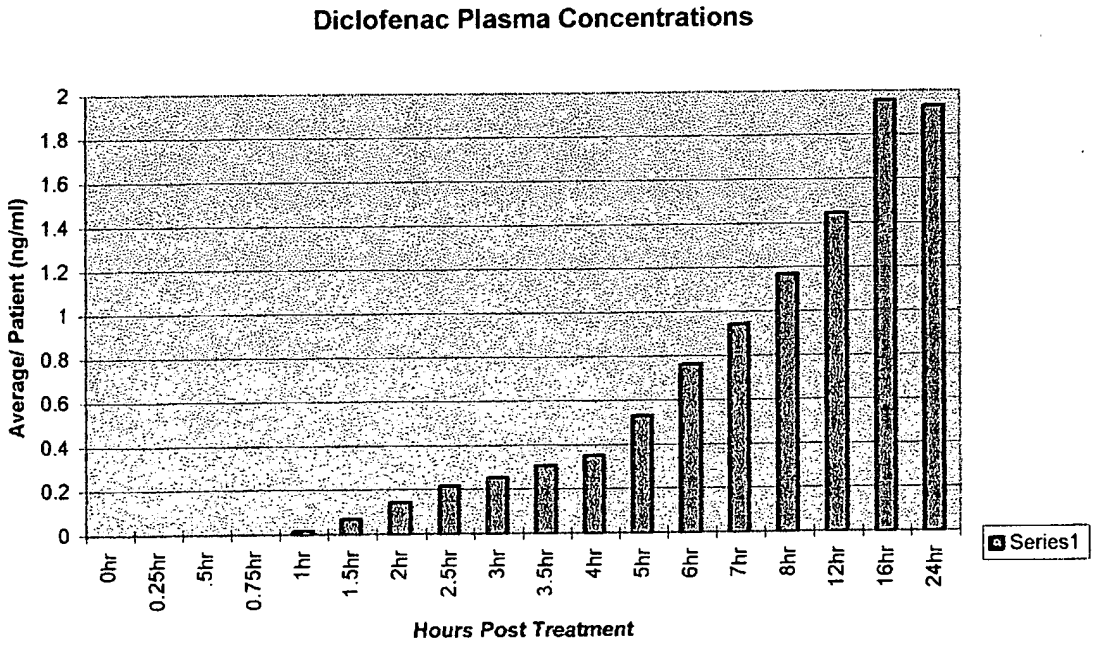
- Pharmacokinetic and bioavailability in normal healthy patients
- Exam possible side effects by patients' symptoms

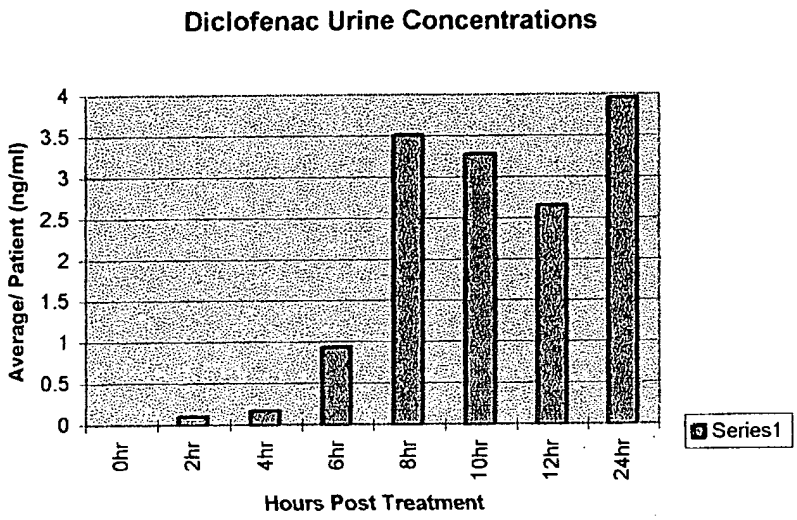
6 patients were asked to volunteer to test the gel

A validated APCI LC/MS/MS method for the determination of diclofenac in human plasma and urine was employed in the Bioanalytical Department of Maxxam Analytics.

Plasma and urine concentrations were measured in all fasted patients at scheduled intervals immediately before and routinely after application to the right anterior knee of the 4cc IPM gel containing 3% diclofenac sodium.

RESULTS: LAM Pharmaceutical's IPM matrix ability to penetrate the skin and deliver an active ingredient systemically is demonstrated below in the patient's diclofenac plasma and urine concentrations.

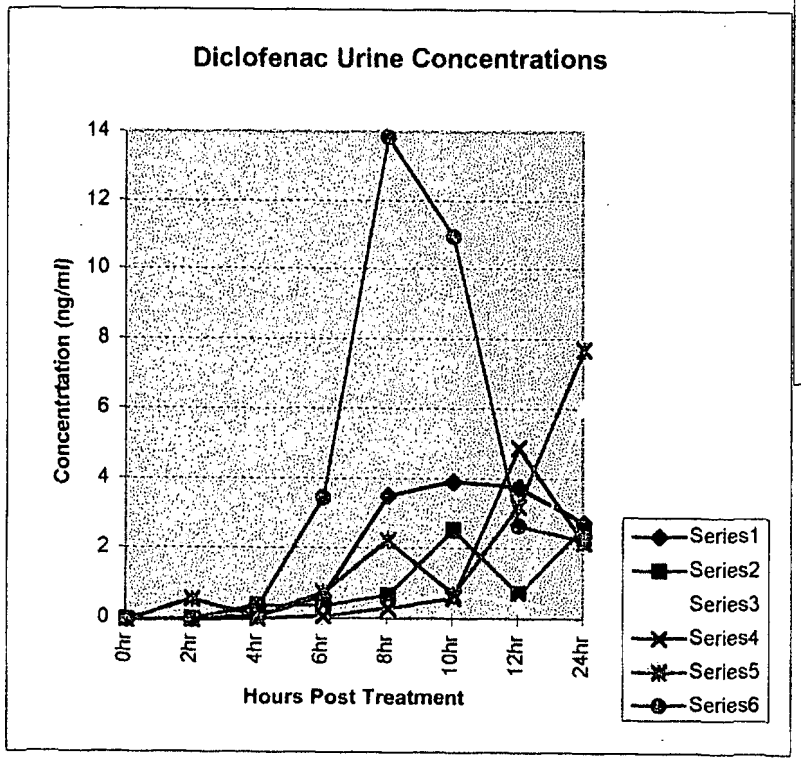


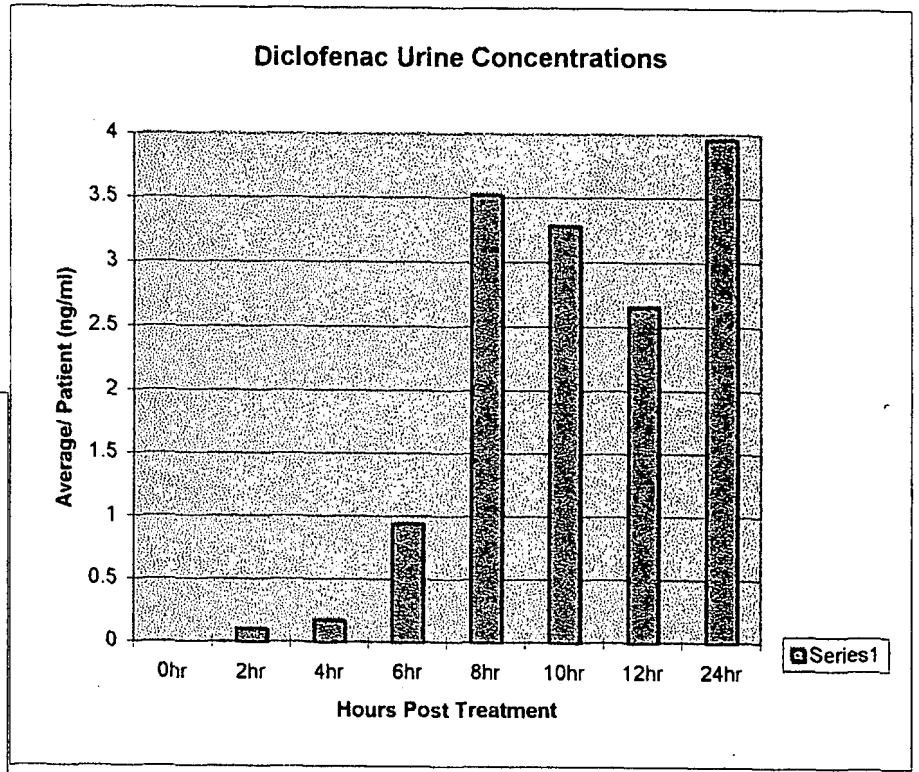


There were no treatment related side effects from the use of the IPM gel.

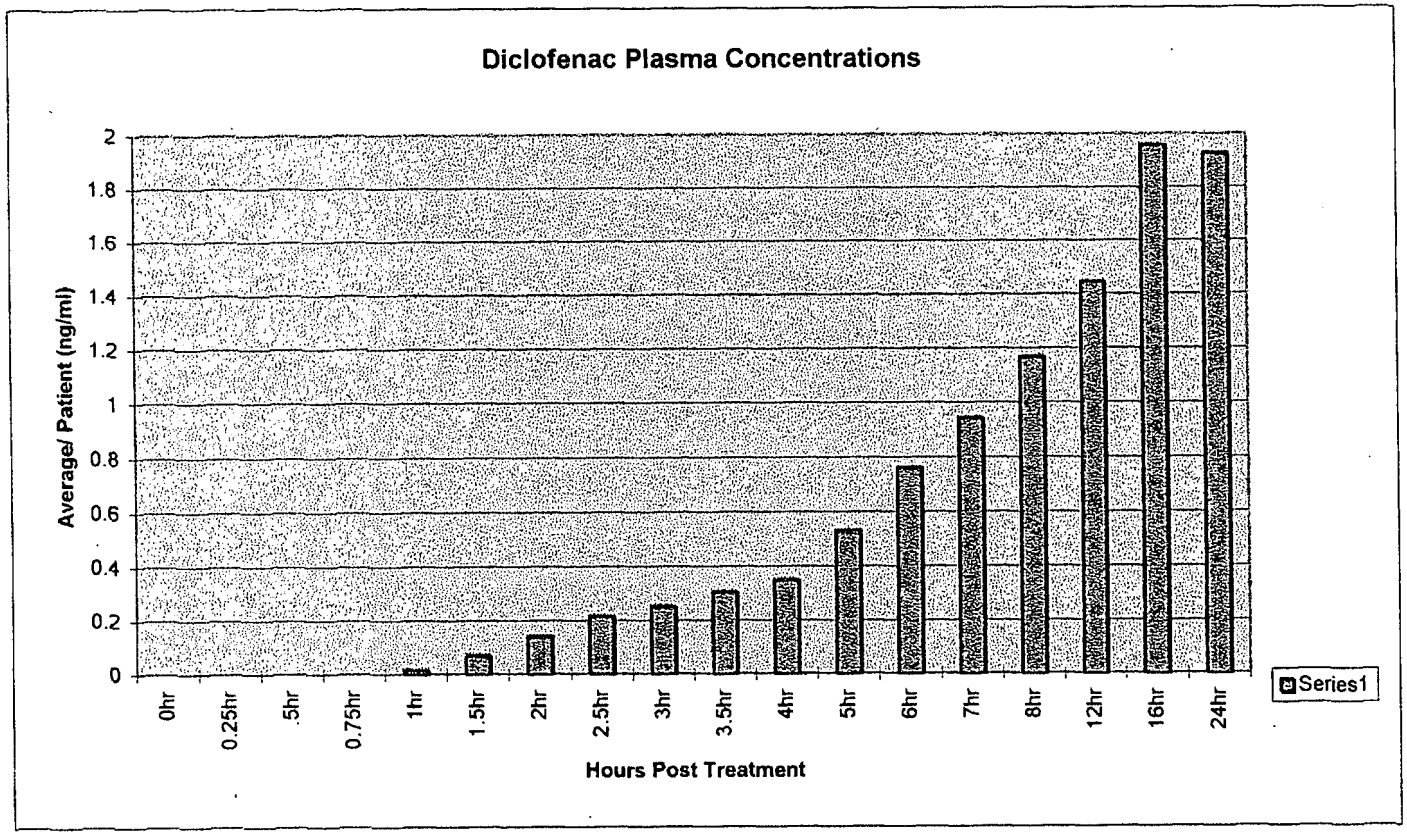
Dr. Alan Drizen

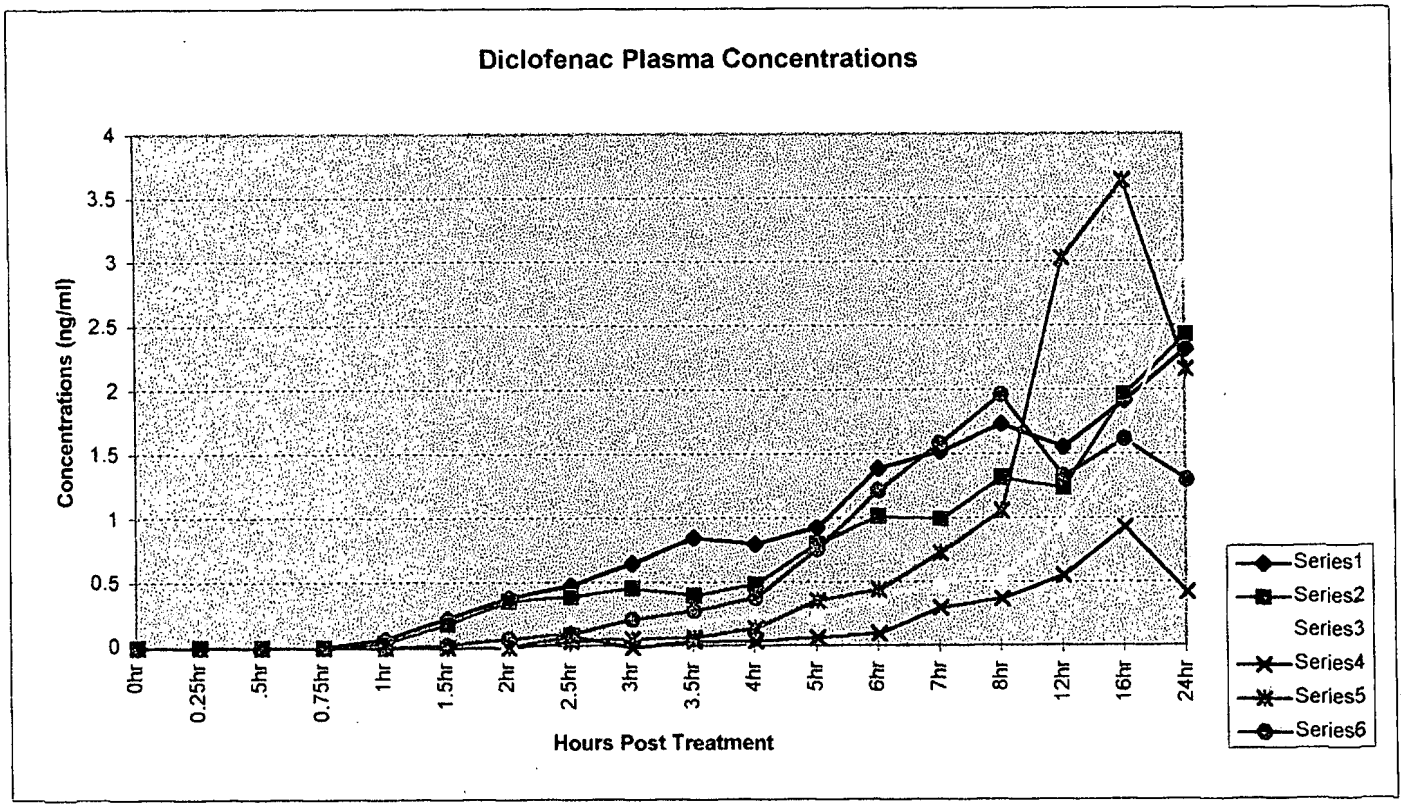
Time		0hr	2hr	4hr	6hr	8hr	10hr	12hr	24hr
Patient	1	0	0.01	0.12	0.7	3.58	3.98	3.83	2.81
	2	0	0.04	0.43	0.4	0.72	2.59	0.79	2.67
	3	0	0	0	0.1	0.32	0.75	0.43	6.04
	4	0	0	0.05	0.1	0.36	0.65	4.95	2.24
	5	0	0.6	0.1	0.8	2.29	0.76	3.28	7.76
	6	0	0	0.38	3.5	13.9	11	2.71	2.27
	aver	0	0.11	0.18	1	3.53	3.29	2.67	3.97





Time (hr)	0hr	0.25hr	.5hr	0.75hr	1hr	1.5hr	2hr	2.5hr	3hr	3.5hr	4hr	5hr	6hr	7hr	8hr	12hr	16hr	24hr
Patient 1	0	0	0	0	0.07	0.23	0.39	0.49	0.66	0.86	0.81	0.94	1.4	1.53	1.75	1.57	1.93	2.33
2	0	0	0	0	0.04	0.19	0.37	0.4	0.47	0.41	0.5	0.81	1.03	1.01	1.33	1.25	1.98	2.44
3	0	0	0	0	0	0	0.05	0.18	0.12	0.18	0.23	0.24	0.38	0.49	0.53	0.94	1.64	2.92
4	0	0	0	0	0	0	0	0.09	0	0.05	0.05	0.08	0.11	0.31	0.38	0.56	0.94	0.43
5	0	0	0	0	0	0	0	0.05	0.07	0.08	0.15	0.37	0.45	0.74	1.07	3.04	3.65	2.17
6	0	0	0	0	0	0.02	0.07	0.11	0.22	0.29	0.39	0.77	1.23	1.6	1.98	1.34	1.63	1.31
aver	0	0	0	0	0.02	0.07	0.15	0.22	0.26	0.31	0.36	0.54	0.77	0.95	1.17	1.45	1.96	1.93




Diclofenac Plasma Concentrations
Concentrations (ng/ml)
4
3.5
3
2.5
2
1.5
1
0.5
0
0hr
0.25hr
.5hr
0.75hr
1hr
1.5hr
2hr
2.5hr
3hr
3.5hr
4hr
5hr
6hr
7hr
8hr
12hr
16hr
24hr
Hours Post Treatment
Series1
Series2
Series3
Series4
Series5
Series6

LAM Pharmaceuticals, Inc.
11190 Biscayne Blvd.
Miami, Florida 33181
Ph: (305) 895-0304
Fax: (305) 895-8616

LAM

A Single Dose Pharmacokinetic And Bioavailability Study of Diclofenac 3% Gel In Normal Healthy Male Volunteers

Protocol No. L.A.M. 01

SPONSOR:

L.A.M. Pharmaceuticals, Inc.
11190 Biscayne Boulevard
Miami, FL 33181-3405

LAM

Final Report
June 30, 1997

A Single Dose Pharmacokinetic And Bioavailability Study of Diclofenac 3% Gel In Normal Healthy Male Volunteers

Protocol No. L.A.M. 01

Compound:	Diclofenac Sodium 3% Gel in Ionic Polymer Matrix (IPM) (Lot #8484) L.A.M. Pharmaceuticals, Inc.
Treatment:	A single dose (4 cc) of Diclofenac Sodium 3% Gel applied topically (4 cc of diclofenac 3% gel contains approximately 120 mg of diclofenac)
Study Dates:	May 14, 1997 - May 16, 1997
Investigator:	Stephen R. Scheinman, M.D.
Study Coordinator:	Debbie Chance-Doonan, M.M.I.S., B.A., C.C.R.C.
Study Site:	South Florida Bioavailability Clinic 11190 Biscayne Boulevard Miami, Florida 33181-3504
Sponsor:	L.A.M. Pharmaceuticals, Inc. 11190 Biscayne Boulevard Miami, Florida 33181-3504
Clinical Monitor:	Allan Driezen, Ph.D. Pharmacokineticist

LAM

Protocol No. L.A.M. 01

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LAM

A Single Dose Pharmacokinetic And Bioavailability Study of Diclofenac 3% Gel In Normal Healthy Male Volunteers

I. Introduction

Diclofenac, as the sodium salt, is a benzeneacetic acid derivative, (2-[(2, 6-dichlorophenyl) aminol] benzeneacetic acid, monosodium salt), Mol. Wt. 318.14, $C_{14}H_{10}Cl_2NNaO_2$. It is a nonsteroidal antiinflammatory drug (NSAID). Orally administered, diclofenac sodium has shown antiinflammatory, analgesic and antipyretic properties in pharmacologic studies. Like other NSAIDs, its system of action is not known; its ability to inhibit prostaglandin synthesis may be related to its antiinflammatory action and ability to relieve pain associated with inflammation. Non-narcotic, it has analgesic effects.

Marketed as Voltaren® Delayed-Release enteric-coated (EC) tablets (Geigy), and available in 25 mg, 50 mg, or 75 mg tablets, diclofenac sodium is currently approved for the acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis of the hip and knee, and anklylosing spondylitis.

Diclofenac sodium delayed-release formulation provides rapid release in the duodenum. Following oral administration in the fasting state, it is completely absorbed from the gastrointestinal tract. It undergoes first-pass metabolism with a systemic availability of 50%. In fasting normal volunteers, peak plasma levels are achieved in 2 hours, with a range from 1 to 4 hours. When taken with food, there may be a delay in the onset of absorbtion of 1 to 4.5 hours, and as long as 10 hours, and a reduction in peak plasma concentration of approximately 40%. Plasma concentrations of diclofenac decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. More than 99% of diclofenac is reversibly bound to human plasma albumin. It shows interindividual differences in pharmacokinetics and pharmacodynamics.

Similarily to other NSAIDs, diclofenac diffuses into and out of the synovial fluid when plasma levels are higher than than those of the synovial fluid. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolilte; the major route of elimination is through hepatic clearance. Elimination of diclofenac metabolites is primarily by the kidneys, with approximately 65% of the dose excreted in the urine, and approximately 35% in the bile. Patients with renal or hepatic impairment have not been shown to exhibit pharmacokinetic differences to date.

Diclofenac sodium is contraindicated in patients in whom aspirin or other NSAIDs have resulted in asthma, urticaria, or other allergic-type reactions. It is contraindicated in patients with hypersensitivite to diclofenac-containing products and those on concomitant diclofenac-containing drug therapy. As with other NSAID therapy, minor upper gastrointestinal problems are common and a risk of gastrointestinal ulcerations, bleeding and perforation also exists. Elevation of liver enzymes may occur.

A market exists for a transdermal product to provide local relief of pain and inflammation or to supercede, supplement, or duplicate the efficacy of orally administered diclofenac sodium. Such a product may avoid the possible side effects of oral dosage which may include headache, dizziness, dyspepsia, peptic ulcers, intestinal bleeding, as well as possible liver enzyme elevations.

L.A.M. Pharmaceuticals, Inc. has developed an ionic polymer matrix (IPM) transdermal delivery system, for topical application of diclofenac sodium (Diclofenac Sodium 3% Gel) directly to the skin of affected sites (knee, foot, neck, back, etc.). Such a transdermal delivery system, aimed directly at specific areas of localized pain and inflammation, would deliver a nonsteroidal antiinflammatory (NSAID) directly to affected areas and could offer distinct advantages over oral therapy. Topical application may provide local relief more rapidly than the systemic route can offer. Gastrointestinal and hepatic implications may be minimized. A single 4 cc application once daily (qd) of diclofenac sodium 3% gel contains approximately 120 mg of diclofenac sodium.

A pilot clinical trial in six (6) normal healthy male volunteers was designed to determine the pharmacokinetics and bioavailability of a single 4 cc dose topical application of L.A.M. diclofenac sodium 3% gel.

II. Objective

The objective of this study was to determine the pharmacokinetics and the bioavailability of a single dose application of L.A.M. diclofenac sodium 3% gel.

III. Study Design

This was an open-label, single center, single phase, single dose, pilot pharmacokinetic and bioavailability study.

Eligibile subjects were identified during a fourteen (14) day screening period prior to dose administration. Subjects reported to the study site on Day -1 to begin the confinement period; confinement continued for 24-hours post dose.

IV. IRB Review

This study was conducted in compliance with the Code of Federal Regulations governing the protection of human subject (21 CFR § 50), institutional review boards (21 CFR § 56), and obligations of clinical investigators (21 CFR § 312). As per federal regulations and International Conference on Harmonization (ICH) guidelines, the Final Protocol and the subject Informed Consent Form were submitted for review and approval to the Independent Institutional Review Board, Inc. (IIRB) prior to the start of the study.

The Form FDA 1572 for this project was signed by Stephen R. Scheinman, M.D. (Principal Investigator). The protocol dated February 26, 1997, and the English and Spanish versions of the subject Informed Consent Form were approved on April 18, 1997 Independent Investigational Review Board Inc. for South Florida Bioavailability Clinic (SFBC).

A letter of approval of this protocol signed by the chairman of the IRB along with a list of IRB members were supplied to L.A.M. Pharmaceuticals, Inc. prior to study initiation. It was the responsibility of the investigator to communicate with the IRB, to make timely and accurate reports on the progress of the trial, and to notify the IRB at the completion of the study.

The IRB was notified of study completion and their Notice of Study Completion dated May 19, 1997 was forwarded to the Sponsor.

V. Facilities

This study was conducted under the supervision of Stephen R. Scheinman, M.D., at South Florida Bioavailability Clinic, 11190 Biscayne Boulevard, Miami, Florida, 33181-3405 (see Appendix VI, Clinical Facility).

All blood chemistries, hematology and urinalyses were carried out by Coral Gables Regional Laboratory Inc., 3233 Palm Avenue (Third Floor), Hialeah, Florida 33012.

Analysis of plasma samples for diclofenac concenrtrations was conducted at Novamann International, Inc., 5540 McAdam Road, Mississauga Ontario, Canada L4Zpi.

Menus and calculation of nutritive values were prepared by Angie Fernandez, M.S., R.D., L.D.N. for SFBC. Meals and snacks were prepared on site as a contract service (see Appendix 8, Study Menus).

L.A.M. Pharmaceuticals, Inc., Novamann International, Inc. and Redfield Laboratories were responsible for the pharmacokinetic and biostatistical evaluation, report preparation and auditing of analytical work for this trial.

VI. Certification of South Florida Bioavailability Clinic

In compliance with the requirements of current Good Clinical Practices, and in particular with the requirements of 21 CRF, Part 314.50(3)(i), Protocol L.A.M. 01 was conducted by South Florida Bioavailability Clinic, Inc.. SFBC did comply as stated with Institutional Review Board Regulations (Part 56), and with Informed Consent Regulations (Part 50), respectively.

In compliance with the requirements of the Generic Drug Enforcement Act of 1992, South Florida Bioavailability Clinic, Inc., (the Company) hereby certifies to the above named person or entity that the Company did not and will not use in any manner the services of any person debarred under subsection (a) or (b) of Section 306 of the Generic Drug Enforcement Act of 1992 (21 U.S.C. 335a)(the "Act"). The Company and affiliated persons of the Company responsible for the development or submission of any applications for the approval of a drug product have not had or been involved in any convictions as described in subsections (a) and (b) of Section 306 of the Act. This certification is made solely for the benefit of the Sponsor named above and may not be used by any other person or entity.

All clinical evaluations in normal healthy volunteers were carried out in full compliance with the requirements of Title 21, Code of Federal Regulations, Parts 312.57 through 312.70, where applicable, concerning the responsibilities of Investigators.

VII. Subject Selection

This study conducted in six (6) normal healthy male volunteers between the ages of 18 and 45 years. All participants were in good general health and qualified according to the inclusion/exclusion criteria of the protocol.

Selected subjects discontinued all medications including over-the-counter preparations and vitamins for seven (7) days prior to and during the course of the study. Efforts were made to screen and select male subjects who exhibited a minimal amount of body hair in the area of the knee. History of hypersensitivity to opioid analgesics, aspirin, or NSAID's prevented participation.

A total of sixteen (16) male volunteers signed the informed consent form and participated in the screening paroacess. Ten (10) qualified volunteers reported for admission to SFBC on Day -1. Of these, two (2) candidates voluntarily withdrew consent and were eliminated from consideration, two (2) were designated as alternate subjects and remained at the study site until the morning of Day 1. They were dismissed prior to dosing.

A panel of six (6) volunteers were entered into this study. Subjects were assigned Subject Numbers 001 through 006 in ascending order according to order of enrollment. The demographics of all screened volunteers are entered in Table 1, Demographic Table of Screened Volunteers. Participants in the trial are listed in Table 2, Demographic Table of Study Subjects.

A. Informed Consent

At the screening visit, the informed consent agreement was read and explained to all subjects in their native language (English and Spanish). All subjects provided written informed consent in accordance with FDA regulations effective August 19, 1991 (CFR 21 § 50) regarding the protection of human subjects.

B. Average Subject Characteristics

Six (6) male subjects between the ages of 36 and 45 years (mean 41 years) entered and completed this study. All subjects were non-smokers, within ±15% of desirable body weight for frame size, and judged to be in good health as determined by their detailed medical histories, complete physical examinations, electrocardiograms, and clinical laboratory tests (including Hepatitis B surface antigen, HIV, and urine drug screen). Four (4) of the six (6) subjects (67%) were medium framed; two (2) subjects (33%) were large framed. Four (4) subjects (67%) were Caucasian; two (2) subjects (33%) were Hispanic.

VIII. Study Conduct

Subjects who met all entrance criteria were admitted to the test facility the evening before dosing (Day -1). Subjects began fasting following a snack at approximately 2100 hours. Subjects fasted for at least eight (8) hours prior to test product application; the fast extended for four (4) hours post-dose. Water was permitted *ad libitum* throughout the study. At approximately 0700 hours on the following morning, Day 1, oral body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure were recorded prior to dosing.

A. Screening Period

Within fourteen (14) days prior to the dose application, eligible male volunteers presented to SFBC for screening and were judged by the Investigator to be healthy. Candidates were healthy, normal, non-smoking males from 18 to 45 years of age. To be eligible, volunteers exhibited all of the inclusion criteria and none of the exclusion criteria. Additionally, they qualified through pre-study screening examinations which included baseline medical history, physical examination, vital signs (blood pressure, pulse, respiration rate and temperature), hematology, blood chemistries, urinalysis, and 12-lead electrocardiogram (EKG), anti-HIV 1, and HBsAg. The physical examination included skin, head, eyes, ears, nose, throat, neck, lymph nodes, chest and lungs, cardiovascular, abdomen, urogenital, spine, extremities, neurological and general psychiatric exams.

Clinical laboratory tests included:

Hematology: Hemoglobin, hematocrit, RBC count, WBC count with differential (percent) and platelet count were measured.

Chemistry: Calcium, sodium, potassium, chloride, inorganic phosphate, uric acid, total protein, albumin, cholesterol, alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, serum glutamic-oxalacetic transaminase (SGOT, AST), serum glutamic-pyruvate transaminase (SGPT;ALT), fasting blood glucose, urea nitrogen (BUN), serum creatinine, CO_2 and triglycerides were measured.

Urinalysis: Color, turbidity, specific gravity, glucose, albumin (protein), bile (urobilinogen), pH, acetone (ketone), and microscopic examination.

The drugs of abuse screen included benzoylmethylecgonine (cocaine), barbiturates, opiates, amphetamines, benzodiazepine, alcohol and cannabinoids. Both serum and alcohol tests were performed at screening.

A total of sixteen (16) male volunteers were screened. Ten (10) qualified volunteers reported for admission to SFBC on Day -1.

B. Study Drug Accountability

Clinical supplies for this project were hand delivered by L.A.M. Pharmaceutical to SFBC on April 29, 1997. Study medication was supplied in clear wide-mouth jars with screw-on tops. All supplies were received in good condition.

As listed below the test materials were received and inventoried by SFBC. All materials were stored at room temperature in the locked SFBC drug room. SFBC received the following:

Identification:	Diclofenac sodium 3% gel (IPM Matrix) (1 ml contains 30 mg/ml of diclofenac sodium)
Date Received:	April 29, 1997
Quantity Received:	12 Jars
Quantity Used:	6 Jars
Quantity Retained:	6 Jars

Retention samples of study drug (six [6] jars) were retained by SFBC to be maintained according to the Federal Register notice dated November 8, 1990, 21 CFR 320.32 and Federal Register notice dated April 8, 1993, Final Rule Effective May 28, 1993, for a period of at least five years.

C. Dose Preparation

Individual dose portions were prepared by the clinical staff within two (2) hours of dosing. Six (6) jars were selected and numbered from 001 to 006. A syringe was marked to correspond to each jar of study drug. A 4 cc portion of the contents of each jar was removed from each jar into a 4 cc syringe and held until dose application. Each 4 cc dose of test product was weighed for accuracy using a Metler Balance.

All clinical supplies were maintained at room temperature in the locked SFBC drug room until immediately prior to dosing.

D. Test Product Administration

One 4 cc transdermal application of L.A.M. diclofenac sodium 3% gel (Lot #8484) was made to the right anterior knee:

Formulation #8484	(4 cc) applied from a sterile syringe to the right anterior knee while subject was in a sitting position.

Each jar of study drug was labeled with the following information:

Diclofenac Sodium 3% Gel
Lot No: #8484
Subject No. _____
Initials: _____
Period No. _____
Date Dispensed: _____

Diclofenac sodium 3% gel contains 30 mg/ml of diclofenac sodium.

Subjects presented for dosing following an eight (8) hour overnight fast. Each volunteer was provided with a pair of gym shorts to wear which provided no interference with the area of application, allowed free access to the right knee, and which allowed easy application of study drug. Subjects were seated in numerical sequence in the SFBC dosing area in straight-back chairs with the right knee exposed for product application.

On Thursday, May 15, 1997, 4 cc of diclofenac sodium 3% gel (Lot #8484) was applied at two (2) minute intervals starting at approximately 0800 hours with Subject Number 001.

Study drug was applied to the clean, dry, non-oily, non-irritated area of the anterior right knee of each subject. The dose was applied to the skin directly from the syringe used for measuring the test product. Coverage was achieved by using a tongue depressor as an applicator to provide even coverage and to avoid contamination and waste. The study drug was applied evenly using sweeping strokes and applying no pressure to the skin. The SFBC drug custodian applied the study drug; surgical gloves were worn. The used tongue depressor was returned to an empty plastic pouch.

The anterior right knee was thoroughly covered in an even application of study drug; the subjects refrained from physical activity to keep the area immobilized as much as possible for approximately six (6) hours. The sites were observed for gel adherence and redness or irritation.

Immediately following the application of study drug, and for six (6) hours post-dose, subjects were encouraged to restrict physical activity and to remain in a sitting position. No food was consumed for four (4) hours post-dose. Subjects were instructed to avoid strenuous or athletic activities during the course of the study. Compliance was monitored by the SFBC study staff. Bathing was not allowed until twenty-four (24) hours post-dose.

For one (1) hour post-dose and at each subsequent blood draw, the site of product application was observed by a trained technician for any change and examined for topical irritation.
or redness. In no subject was change of any kind observed. The study drug remained in place and was undisturbed for twenty-four (24) hours, or until the subjects bathed, but not before the end of the 24-hour period. Again at 24-hours post-dose, the site of application was examined for topical irritation. No skin irritation was observed.

Qualified study personnel were present for dosing and remained at the study site for several hours following the administration. The Principal Investigator was available for consultation twenty-four (24) hours a day throughout the course of the study.

No food was consumed for four (4) hours post-dose. Meals were served following blood draws at 4 and 8 hours post study drug application. A snack was served at approximately 2100 hours (see Appendix IV, Study Meals). During the period of confinement, volunteers consumed no food or beverages (other than water) except during the designated meal periods. Standardized meals were served.

Subjects remained at the study center for twenty-four (24) hours post-dose on Study Day 2, until completion of all study procedures. Following the 24 hour blood sample collection on Day 2, each subject underwent a physical exam as for Pre-Study, including a 12-lead EKG. All vital signs were repeated. Clinical laboratory tests as for Pre-Study were performed 24 hours following the dose, with the exception of urine drug screen, blood alcohol test, HIV and Hepatitis B tests. There were no clinically significant findings; all clinical laboratory values were normal or not clinically significant.

Complete details on dosing, blood sampling times, and vital signs are provided for all subjects in Individual Case Report Forms, Appendix XI.

Comprehensive information relative to subject selection, exclusion criteria, sample collection, and data analysis can be found in the study protocol, included as Appendix I.

E. Vital Signs

At screening, vital signs (blood pressure, pulse, respiration rate and temperature), as well as height and weight, were measured and recorded. Seated systolic and diastolic blood pressure, heart rate, respiratory rate, oral body temperature, sitting radial pulse, weight, height and frame size were again recorded prior to drug application (0.0 hour) and at 2.0, 4.0, 8.0, 12.0 and 24.0 hours post-dose.

All vital signs were repeated on Day 2, prior to dismissal from the clinic (24.0 hours post-dose).

F. Blood And Urine Sample Collection and Handling

A 10 ml baseline blood sample was obtained by venipuncture immediately preceding (0.0 hours) study drug administration. A total of eighteen (18) 10 ml blood samples (180 ml total volume) were collected by venipuncture at 0.0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 12.0, 16.0 and 24.0 hours following study drug application. Blood volume for screening and post-study evaluations totaled 30 ml for a cumulative study total of 210 ml of blood.

During the study, all whole blood samples were collected in lavender top vacuum tubes containing EDTA solution; samples were centrifuged at 2000 rpm at 4°C for 15 minutes. The resultant plasma from each sample was separated into two (2) polypropylene specimen transfer vials and stored at -20°C until shipped to the analytical facility.

Clinical laboratory tests as for Pre-Study were also performed 24 hours following the dose, with the exception of urine drug screen, blood alcohol test, HIV and Hepatitis B tests.

Subjects were asked to empty their bladders immediately prior to drug administration. During subsequent collection interval hours, subjects could void urine on more than one occasion. Urine samples were collected for determination of diclofenac sodium concentration during eight (8) intervals: (pre-dose) at 0.0-2.0, 2.0-4.0, 4.0-6.0, 6.0-8.0, 8.0-10.0, 10.0-12.0, 12.0-24.0. The clock time of collection was recorded for all subjects.

All urine containers were labeled at the site with the subject initial, number, period number, and urine collection time. The total volume and pH of each urine interval was recorded. During each collection interval, two (2) 15ml aliquot were transferred into chilled polypropylene tubes which were stored at -20°C. Multiple voids were recorded during any collection interval.

G. Sample Shipment

The frozen plasma and urine samples were packed on dry ice and shipped according to protocol on May 28, 1997 to:

Novamann International, Inc.
5540 McAdam Road
Mississauga Ontario, Canada L4Zpi

The Sponsor and the analytical laboratory were notified in advance of the shipping schedule. The samples were received frozen and in good condition.

H. Test Site Assessment

For one (1) hour following drug application the anterior knee area was observed by study staff for topical irritation. Study drug remained evident on the surface of the skin until absorbed. There was no evidence of change, redness or irritation at the site of application for any subject.

IX. Adverse Experiences

During the Study, no adverse experiences were reported by any volunteers, nor observed by SFBC staff.

X. Protocol Exceptions

This project was faithfully performed in conformance with the study protocol. There were no deviations from the protocol.

XI. Summary

L.A.M. diclofenac sodium 3% gel (4 cc) in a matrix transdermal system (IPM) was applied to the anterior right knee of six (6) healthy male volunteers in this open-label, single center, single phase, single dose pharmacokinetics and bioavailability study.

Throughout this study, the test product was well tolerated by all participants. Clinical laboratory tests and physical exams performed at the completion of the study revealed no clinically significant abnormalities. No adverse events were reported.

L.A.M. PHARMACEUTICALS, INC.
PROTOCOL L.A.M. 01

TABLE 1

DEMOGRAPHIC TABLE OF SCREENED SUBJECTS

Subject Number	Screen Number	Subject Initials	Sex	Age	D.O.B.*	Race	Height cm.	Weight kg.	Frame
	001	MJR	M	40	01/26/57	H	165.1	76.4	M
	002	EFL	M	22	04/04/75	H	182.9	83.2	M
001	003	CCM	M	36	03/19/61	C	175.3	82.3	M
002	004	RGM	M	45	09/28/51	C	170.2	84.5	L
	005	JAS	M	38	05/02/58	H	175.3	83.6	S
003	006	J-R	M	44	05/22/52	C	182.9	82.3	M
004	007	J-D	M	39	09/14/57	H	170.2	84.5	L
	008	DFP	M	32	11/02/64	C	177.8	83.2	M
	009	I-Z	M	37	01/03/60	C	170.2	73.6	S
	010	SRA	M	24	08/23/72	H	167.6	63.6	S
	011	RLS	M	25	12/24/71	H	172.7	77.3	M
005	012	FJC	M	40	04/03/57	H	172.7	81.8	M
006	013	RJC	M	41	03/02/56	C	172.7	70.0	M
	014	CES	M	35	05/17/61	C	172.7	77.3	M
	015	AOC	M	42	02/03/55	H	162.6	69.1	M
	016	S-C	M	45	09/25/51	H	170.2	68.2	N/D

RACE:

A= Asian
B= Black
C= Caucasian
H= Hispanic
O= Other

* Date of Birth

L.A.M. PHARMACEUTICALS, INC.
PROTOCOL L.A.M. 01

TABLE 2

DEMOGRAPHIC TABLE OF ENROLLED SUBJECTS

Subject Number	Screen Number	Subject Initials	Sex	Age	D.O.B.	Race	Height cm.	Weight kg.	Frame
001	003	CCM	M	36	03/19/61	C	175.3	82.3	M
002	004	RGM	M	45	09/28/51	C	170.2	84.5	L
003	006	J-R	M	44	05/22/52	C	182.9	82.3	M
004	007	J-D	M	39	09/14/57	H	170.2	84.5	L
005	012	FJC	M	40	04/03/57	H	172.7	81.8	M
006	013	RJC	M	41	03/02/56	C	172.7	70.0	M
Mean •				41			174.0	80.9	
Standard Deviation •				6.4			13.2	8.9	

RACE:

A= Asian B= Black C= Caucasian H= Hispanic O= Other

• = Completed Subjects

TABLE 3

DOSE ADMINISTRATION TABLE

Subject Number	Subject Initials	Dosage	Area of Application	Planned Dose Time	Actual Dose Time
001	CCM	4 ml	Right knee	0801	0801
002	RGM	4 ml	Right knee	0803	0803
003	J-R	4 ml	Right knee	0805	0805
004	J-D	4 ml	Right knee	0807	0807
005	FJC	4 ml	Right knee	0809	0809
006	RJC	4 ml	Right knee	0811	0811

Labeling Guidance
Revised February 199 5

DICLOFENAC SODIUM DELAYED-RELEASE TABLETS

DESCRIPTION

Diclofenac sodium is a benzene-acetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt. The structural formula is:

M.W. 318.14 C $_{14}H_{10}Cl_2NNaO_2$

Diclofenac sodium, is a faintly yellowish white to light beige, virtually odorless, slightly hygroscopic crystalline powder. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in water and practically insoluble in chloroform and in dilute acid. The n-octanol/water partition coefficient is 13.4 at pH 7.4 and 1545 at pH 5.2. Diclofenac sodium has a dissociation constant (pKa) of 4.0 ± 0.2 at 25 °C in water.

Each enteric-coated tablet for oral administration contains ____mg of diclofenac sodium. In addition, each tablet contains the following inactive ingredients...

[*Note To The Firm:* We refer you to USP General Chapter <1091> for guidance concerning the citing of all inactive ingredients.]

CLINICAL PHARMACOLOGY

Pharmacodynamics

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity.

Pharmacokinetics

Diclofenac sodium delayed-release tablets are in a pharmaceutic formulation that resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH-environment in the duodenum. Its pattern of drug release and

absorption, as illustrated below:

± 1 SD plasma diclofenac concentrations after a single dose of a 50 mg diclofenac sodium delayed-release tablet (N=38)

Absorption

When diclofenac sodium delayed-release tablets are administered orally after fasting, diclofenac is completely absorbed from the gastrointestinal tract. Of this, only 50% of the absorbed dose of diclofenac from diclofenac sodium is systemically available, due to first-pass metabolism. Peak plasma levels are achieved in 2 hours in fasting normal volunteers, with a range from 1 to 4 hours. The area-under-the-plasma-concentration curve (AUC) is dose-proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose-proportional and are approximately 1.0, 1.5, and 2 µg/mL for 25 mg, 50 mg and 75 mg doses, respectively. It should be noted that the administration of several individual diclofenac sodium tablets may not yield equivalent results in peak concentration as the administration of one tablet of a higher strength. This is probably due to the staggered gastric emptying of tablets into the duodenum. After repeated oral administration of diclofenac sodium 50 mg b.i.d., diclofenac did not accumulate in plasma.

When diclofenac sodium is taken with food, there is usually a delay in the onset of absorption of 1 to 4.5 hours, with delays as long as 10 hours in some patients, and a reduction in peak plasma levels of approximately 40%. The extent of absorption of diclofenac, however, is not significantly affected by food intake.

Distribution

Plasma concentrations of diclofenac decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of

distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac is reversibly bound to human plasma albumin.

A 4-week study, comparing plasma level profiles of diclofenac (diclofenac sodium 50 mg b.i.d.) in younger (26 to 46 years) versus older (66 to 81 years) adults, did not show differences between age groups (10 patients per age group).

As with other NSAIDs, diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism and Elimination

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile.

Conjugates of unchanged diclofenac account for 5 to 10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. Conjugates of the principal metabolite account for 20 to 30% of the dose excreted in the urine and for 10 to 20% of the dose excreted in the bile. Conjugates of three other metabolites together account for 10 to 20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

Patients with Renal and/or Hepatic Impairment

To date, no differences in the pharmacokinetics of diclofenac have been detected in studies of patients with renal (50 mg intravenously) or hepatic impairment (100 mg oral solution). In patients with renal impairment (N=5, creatinine clearance 3 to 42 mL/min), AUC values and elimination rates were comparable to those in healthy subjects. In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, N=10), diclofenac concentrations and urinary elimination values were comparable to those in healthy subjects.

Clinical Studies

Osteoarthritis:
Diclofenac sodium was evaluated for the management of the signs and symptoms of osteoarthritis of the hip or knee in a total of 633 patients treated for up to 3 months in placebo and active-controlled clinical trials against aspirin (N=449), and naproxen (N=92). Diclofenac sodium was given both in variable (100 to 150 mg/day) and fixed (150 mg/day) dosing schedules on either b.i.d. or t.i.d. dosing regimens. In these trials, diclofenac sodium was found to be comparable to 2400 to 3600 mg/day of aspirin or

500 mg/day of naproxen. Diclofenac was effective when administered as either b.i.d. or t.i.d. dosing regimens.

Rheumatoid Arthritis:

Diclofenac sodium was evaluated for managing the signs and symptoms of rheumatoid arthritis in a total of 468 patients treated for up to 3 months in placebo- and active- controlled clinical trials against aspirin (N=290), and ibuprofen (N = 74). Diclofenac sodium was given in a fixed (150 or 200 mg/day) dosing schedule as either b.i.d. or t.i.d. dosing regimens. Diclofenac sodium was found to be comparable to 3600 to 4800 mg/day of aspirin, and 2400 mg/day of ibuprofen. Diclofenac sodium was used b.i.d. or t.i.d., administering 150 mg/day in most trials, but 50 mg q.i.d. (200 mg/day) was also studied.

Ankylosing Spondylitis:

Diclofenac sodium was evaluated for the management of the signs and symptoms of ankylosing spondylitis in a total of 132 patients in one active controlled clinical trial against indomethacin (N=130). Both diclofenac sodium and indomethacin patients were started on 25 mg t.i.d. and were permitted to increase the dose 25 mg per day each week to a maximum dose of 125 mg/day. Diclofenac sodium 75 to 125 mg/day was found to be comparable to indomethacin 75 to 125 mg/day.

G.I. Blood Loss/Endoscopy Data:

G.I. blood loss and endoscopy studies were performed with diclofenac sodium delayed-release [enteric-coated] tablets that, unlike immediate-release tablets, do not dissolve in the stomach where the endoscopic lesions are primarily seen. A repeat-dose endoscopy study, in patients with rheumatoid arthritis or osteo-arthritis treated with diclofenac sodium delayed-release tablets 75 mg b.i.d. (N=101), or naproxen (immediate-release tablets) 500 mg b.i.d. (N=103) for three months, resulted in a significantly smaller number of patients with an increase in endoscopy score from baseline and a significantly lower mean endoscopy score after treatment in the diclofenac sodium treated patients. Two repeat-dose endoscopic studies, in normal volunteers, showed that daily doses of diclofenac sodium delayed-release tablets 75 or 100 mg (N=6 and 14, respectively) for 1 week caused fewer gastric lesions, and those that did occur had lower scores than those observed following daily 500 mg doses of naproxen (immediate-release tablets). In healthy subjects, the daily administration of 150 mg of diclofenac sodium (N=8) for 3 weeks resulted in a mean fecal blood loss of less than that observed with 3 g of aspirin daily (N=8). In four repeat-dose studies, mean fecal

blood loss with 150 mg of diclofenac was also less than that observed with 750 mg of naproxen (n=8 and 6) or 150 mg of indomethacin (N=8 and 6) . *The clinical significance of these*

findings is unknown since there is no evidence available to indicate that diclofenac sodium is less likely than other drugs of its class to cause serious gastrointestinal lesions when used in chronic therapy.

Individualization of Dosage

Diclofenac, like other NSAIDs, shows interindividual differences in both pharmacokinetics and clinical response (pharmacodynamics). Consequently, the recommended strategy for initiating therapy is to use a starting dose likely to be effective for the majority of patients and to adjust dosage thereafter based on observation of diclofenac's beneficial and adverse effects.

In patients weighing less than 60 kg (132 lbs), or where the severity of the disease, concomitant medication, or other diseases warrant, the maximum recommended total daily dose of diclofenac should be reduced. Experience with other NSAIDs has shown that starting therapy with maximal doses in patients at increased risk due to renal or hepatic disease, low body weight (<60 kg), advanced age, a known ulcer diathesis, or known sensitivity to NSAID effects, is likely to increase frequency of adverse reactions and is not recommended (see PRECAUTIONS).

Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis:

The usual starting dose of diclofenac sodium delayed-release tablets for patients with osteoarthritis, is 100 to 150 mg/day, using a b.i.d. or t.i.d. dosing regimen. In two variable-dose clinical trials in osteoarthritis, of 266 patients started on 100 mg/day, 176 chose to increase the dose to 150 mg/day. Dosages above 150 mg/day have not been studied in patients with osteoarthritis.

The usual starting dose of diclofenac sodium for most patients with rheumatoid arthritis is 150 mg/day, using a b.i.d. or t.i.d. dosing regimen. Patients requiring more relief of pain and inflammation may increase the dose to 200 mg/day. In clinical trials, patients receiving 200 mg/day were less likely to drop from the trial due to lack of efficacy than patients receiving 150 mg/day. Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis because of increased risk of adverse events.

The recommended dose of diclofenac sodium delayed-release tablets for patients with ankylosing spondylitis is 100 to 125 mg/day, using a q.i.d. dosing regimen (see DOSAGE AND ADMINISTRATION regarding the 125 mg/day dosage regimen). In a variable-dose clinical trial, of 132 patients started on 75 mg/day, 122 chose to increase the dose to 125 mg/day. Dosages

above 125 mg/day have not been studied in patients with ankylosing spondylitis.

INDICATIONS AND USAGE

Diclofenac sodium delayed-release tablets are indicated for the acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

CONTRAINDICATIONS

Diclofenac sodium delayed-release tablets are contraindicated in patients with hypersensitivity to the product. Diclofenac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac have been reported in such patients.

WARNINGS

Gastrointestinal Effects

Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving diclofenac. Physicians and patients should therefore remain alert for ulceration and bleeding in patients treated chronically with diclofenac even in the absence of previous G.I. tract symptoms. It is recommended that patients be maintained on the lowest dose of diclofenac possible consistent with achieving a satisfactory therapeutic response.

Risk of G.I. Ulcerations, Bleeding and Perforation with/NSAID Therapy: Serious gastrointestinal toxicity such bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous G.I. tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper G.I. ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients for 3 to 6 months, and in about 2 to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious G.I. toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious G.I. events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have

been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal G.I. events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of G.I. toxicity.

Hepatic Effects

As with other NSAIDs, elevations of one or more liver tests may occur during diclofenac therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations, (i.e., less than 3 times the ULN [=the Upper Limit of the Normal range]), or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the hepatic enzymes, ALT (SGPT) is the one recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during diclofenac sodium treatment. In a large, open, controlled trial meaningful elevations of ALT and/or AST occurred in about 4% of 3700 patients treated for 2 to 6 months, including marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3 to 8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

In addition to the enzyme elevations seen in clinical trials, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, have been reported.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label), that involved 3700 patients monitored first at 8 weeks and 1200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were

detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with diclofenac. Based on this experience, if diclofenac is used chronically, the first transaminase measurement should be made no later than 8 weeks after the start of diclofenac treatment. As with other NSAIDs, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), diclofenac should be discontinued.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

PRECAUTIONS

General

Allergic Reactions: As with other NSAIDs, allergic reactions including anaphylaxis, have been reported with diclofenac. Specific allergic manifestations consisting of swelling of eyelids, lips, pharynx and larynx, urticaria, asthma, and bronchospasm, sometimes with a concomitant fall in blood pressure (severe at times) have been observed in clinical trials and/or the marketing experience with diclofenac. Anaphylaxis has rarely been reported from foreign sources; in U.S. clinical trials with diclofenac in over 6000 patients, 1 case of anaphylaxis was reported. In controlled clinical trials, allergic reactions have been observed at an incidence of 0.5% These reactions can occur without prior exposure to the drug.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking diclofenac. Therefore, as with other NSAIDs, diclofenac should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Renal Effects: As a class, NSAIDs have been associated with renal papillary necrosis and other abnormal renal pathology in long-term administration to animals. In oral diclofenac studies in animals, some evidence of renal toxicity was noted. Isolated incidents of papillary necrosis were observed in a few animals at high doses (20 to 120 mg/kg) in several baboon subacute studies.

In patients treated with diclofenac, rare cases of interstitial nephritis and papillary necrosis have been reported (see ADVERSE REACTIONS).

A second form of renal toxicity, generally associated with NSAIDs, is seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate overt renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Cases of significant renal failure in patients receiving diclofenac have been reported from marketing experience, but were not observed in over 4000 patients in clinical trials during which serum creatinine and BUN values were followed serially. There were only 11 patients (0.3%) whose serum creatinine and concurrent serum BUN values were greater than 2.0 mg/dL and 40 mg/dL, respectively, while on diclofenac (mean rise in the 11 patients: creatinine 2.3 mg/dL and BUN 28.4 mg/dL).

Since diclofenac metabolites are eliminated primarily by the kidneys, patients with significantly impaired renal function should be more closely monitored than subjects with normal renal function.

Porphyria: The use of diclofenac in patients with hepatic porphyria should be avoided. To date, one patient has been described in whom diclofenac probably triggered a clinical attack of porphyria. The postulated mechanism, demonstrated in rats, for causing such attacks by diclofenac, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

Information for Patients

Diclofenac, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding and, more rarely, liver toxicity (see WARNINGS, Hepatic Effects) which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis and have a major roll in the management of pain but they also may be commonly employed for conditions that are less

serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Because serious G.I. tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS, *Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy)*. If diclofenac is used chronically, patients should also be instructed to report any signs and symptoms that might be due to hepatotoxicity of diclofenac; these symptoms may become evident between visits when periodic liver laboratory tests are performed (see WARNINGS, Hepatic Effects).

Drug Interactions

Aspirin: Concomitant administration of diclofenac and aspirin is not recommended because diclofenac is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations, peak plasma levels, and AUC values.

Anticoagulants: While studies have not shown diclofenac to interact with anticoagulants of the warfarin type, caution should be exercised, nonetheless, since interactions have been seen with other NSAIDs. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function as well, concurrent therapy with all NSAIDs, including diclofenac, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of diclofenac may increase serum concentrations of digoxin and methotrexate and increase cyclosporine's nephrotoxicity. Patients who begin taking diclofenac or who increase their diclofenac dose or any other NSAID while taking digoxin, methotrexate, or cyclosporine may develop toxicity characteristics of these drugs. They should be observed closely, particularly if renal function is impaired. In

the case of digoxin, serum levels should be monitored.

Lithium: Diclofenac decreases lithium renal clearance and increases lithium plasma levels. In patients taking diclofenac and lithium concomitantly, lithium toxicity may develop.

Oral Hypoglycemics: Diclofenac does not alter glucose metabolism in normal subjects nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experiences of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac that necessitated changes in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Diuretics: Diclofenac and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7 to 10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline or digitoxin did not significantly affect the peak levels and AUC values of diclofenac.

Protein Binding

In vitro, diclofenac interferes minimally or not at all with the protein binding of salicylic acid (20% decrease in binding), tolbutamide, prednisolone (10% decrease in binding), or warfarin. Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence *in vitro* on the protein binding of diclofenac in human serum.

Drug/Laboratory Test Interactions

Effect on Blood Coagulation: Diclofenac increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1

second in both instances, however, and are unlikely to be clinically important. Diclofenac is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day (12 mg/m ^{2}/day, approximately the human dose), have revealed no significant increases in tumor incidence. There was a slight increase in benign mammary fibroadenomas in mid-dose-treated (0.5 mg/kg/day or 3 mg/m ^{2}/day) female rats (high-dose females had excessive mortality), but the increase was not significant for this common rat tumor. A two-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m ^{2}/day) in males and 1 mg/kg/day (3 mg/m ^{2}/day) in females did not reveal any oncogenic potential. Diclofenac sodium did not show mutagenic activity in *in vitro* point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems, and was nonmutagenic in

several mammalian *in vitro* and *in vivo* tests, including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. Diclofenac sodium administered to male and female rats at 4 mg/kg/day (24 mg/m ^{2}/day) did not affect fertility.

Teratogenic Effects

There are no adequate and well controlled studies in pregnant women. Diclofenac should be used during pregnancy only if the benefits to the mother justify the potential risk to the fetus.

Pregnancy Category B: Reproduction studies have been performed in mice given diclofenac sodium (up to 20 mg/kg/day, or 60 mg/m^2/day) and in rats and rabbits given diclofenac sodium (up to 10 mg/kg/day, or 60 mg/m ^{2}/day for rats, and 80 mg/m ^{2}/day for rabbits), and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice and rats.

Labor and Delivery

The effects of diclofenac on labor and delivery in pregnant women are unknown. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of diclofenac during late pregnancy should be avoided and, as with other nonsteroidal anti-inflammatory drugs, it is possible that diclofenac may inhibit uterine contraction.

Nursing Mothers

Diclofenac has been found in the milk of nursing mothers. As with other drugs that are excreted in milk, diclofenac is not recommended for use in nursing women.

Pediatric Use

Safety and effectiveness of diclofenac in pediatric patients have not been established.

Geriatric Use

Of the more than 6000 patients treated with diclofenac in U.S. trials, 31% were older than 65 years of age. No overall difference was observed between efficacy, adverse event or pharmacokinetic profiles of older and younger patients. As with any NSAID, the elderly are likely to tolerate adverse reactions

less well than younger patients.

ADVERSE REACTIONS

Adverse reaction information is derived from blinded, controlled and open-label clinical trials, as well as worldwide marketing experience. In the description below, rates of more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally not possible.

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks with diclofenac sodium delayed-release tablets. By far the most common adverse effects were gastrointestinal symptoms, most of them minor, occurring in about 20%, and leading to discontinuation in about 3%, of patients. Peptic ulcer or G.I. bleeding occurred in clinical trials in 0.6% (95%-confidence interval: 0.2% to 1%) of approximately 1800 patients during their first 3 months of diclofenac treatment and 1.6% (95%- confidence interval: 0.8% to 2.4%) of approximately 800 patients followed for 1 year.

Gastrointestinal symptoms were followed in frequency by central nervous system side effects such as headache (7%) and dizziness (3%).

Meaningful (exceeding 3 times the Upper Limit of Normal) elevations of ALT (SGPT) or AST (SGOT) occurred at an overall rate of approximately 2% during the first 2 months of diclofenac sodium treatment. Unlike aspirin-related elevations, which occur more frequently in patients with rheumatoid arthritis, these elevations were more frequently observed in patients with osteoarthritis (2.6%) than in patients with rheumatoid arthritis (0.7%). Marked elevations (exceeding 8 times the ULN) were seen in 1% of patients treated for 2 to 6 months (see WARNINGS, Hepatic Effects).

The following adverse reactions were reported in patients treated with diclofenac:

Incidence Greater Than 1% - Causal Relationship Probable : (All derived from clinical trials)

Body as a Whole: Abdominal pain or cramps,* headache,* fluid retention, abdominal distention.

Digestive: Diarrhea,* indigestion,* nausea,* constipation,* flatulence, liver tests abnormalities,* PUB, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer (see above and also WARNINGS).

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special Senses: Tinnitus.

* Incidence 3% to 9% (incidence of unmarked reactions is 1 to 3%).

Incidence Less Than 1% - Causal Relationship Probable :
The following reactions have been reported in patients taking diclofenac under circumstances that do not permit a clear attribution of the reaction to diclofenac. These reactions are being included as alerting information for physicians. Adverse reactions reported only in *worldwide marketing experience* or in the literature, not seen in clinical trials, are considered rare and are italicized.

Body as a Whole: Malaise, swelling of lips and tongue, photosensitivity, *anaphylaxis*, anaphylactoid reactions.

Cardiovascular: Hypertension, congestive heart failure.

Digestive: Vomiting, jaundice, melena, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, *hepatic necrosis*, appetite change, pancreatitis with or without concomitant hepatitis, *colitis*.

Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, *hemolytic anemia*, *aplastic anemia*, *agranulocytosis*, purpura, *allergic purpura*.

Metabolic and Nutritional Disorders: Azotemia.

Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability, *aseptic meningitis*

Respiratory: Epistaxis, asthma, laryngeal edema.

Skin and Appendages: Alopecia, urticaria, eczema, dermatitis, *bullous eruption*, *erythema multiforme major*, angioedema, *Stevens-Johnson syndrome*.

Special Senses: Blurred vision, taste disorder, reversible hearing loss, scotoma.

Urogenital: *Nephrotic syndrome*, proteinuria, *oliguria*, *interstitial nephritis*, *papillary necrosis*, *acute renal failure*.

Incidence Less Than 1% - Causal Relationship Unknown
(Adverse reactions reported only in worldwide marketing experience or in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Chest pain.

Cardiovascular: Palpitations, *flushing*, tachycardia, premature ventricular contractions, myocardial infarction.

Digestive: Esophageal lesions.

Hemic and Lymphatic: *Bruising*.

Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss*.

Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination*, convulsions, *disorientation*, *psychotic reaction*.

Respiratory: Dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages: Excess perspiration, *exfoliative dermatitis.*
Special Senses: Vitreous floaters, night blindness, amblyopia.
Urogenital: Urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

OVERDOSAGE

Worldwide reports on overdosage with diclofenac cover 66 cases. In approximately one-half of these reports of overdosage, concomitant medications were also taken. The highest dose of diclofenac was 5 g in a 17-year-old male who suffered loss of consciousness, increased intracranial pressure, aspiration pneumonitis, and died 2 days after overdose. The next highest doses of diclofenac were 4 g and 3.75 g. The 24-year-old female who took 4 g and the 28- and 42-year-old females, each of whom took 3.75 g, did not develop any clinically significant signs or symptoms. However, there was a report of a 17-year-old female who experienced vomiting and drowsiness after an overdose of 2.37 g of diclofenac.

Animal LD_{50} values show a wide range of susceptibilities to acute overdosage, with primates being more resistant to acute toxicity than rodents (LD_{50} in mg/kg--rats, 55; dogs, 500; monkeys, 3200).

In case of acute overdosage it is recommended that the stomach be emptied by vomiting or lavage. Forced diuresis may theoretically be beneficial because the drug is excreted in the urine. The effect of dialysis or hemoperfusion in the elimination of diclofenac (99% protein-bound: see CLINICAL PHARMACOLOGY) remains unproven. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption of diclofenac.

DOSAGE AND ADMINISTRATION

Diclofenac sodium may be administered as 25 mg, 50 mg or 75 mg delayed-release tablets. Regardless of the indication, the dosage of diclofenac should be individualized to the lowest effective dose to minimize adverse effects (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

Osteoarthritis: The recommended dosage is 100 to 150 mg/day in divided doses, 50 mg b.i.d. or t.i.d. or 75 mg b.i.d. Dosages above 150 mg/day have not been studied in patients with osteoarthritis.

Rheumatoid Arthritis: The recommended dosage is 150 to 200 mg/day in divided doses, 50 mg t.i.d. or q.i.d. or 75 mg b.i.d. Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis.

Ankylosing Spondylitis: The recommended dosage is 100 to

125 mg/day administered as 25 mg q.i.d. with an extra 25 mg dose at bedtime if necessary. Dosages above 125 mg/day have not been studied in patients with ankylosing spondylitis.

HOW SUPPLIED

-Established name
-Dosage form and strength
-Color, shape, debossing, scoring
-Packaging
-NDC #
-Recommended storage conditions and dispensing recommendations

Caution: Federal law prohibits dispensing without prescription.

Name and place of business of manufacturer and/or distributor.

Revised-month/year